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(54) Title: PROCESS FOR PREPARING ZOLMITRIPTAN COMPOUNDS

(57) Abstract: In particular, zolmitriptan or a pharmaceutically acceptable salt thereof, which includes a) Preparation of the diazonium salt of the aniline hydrochloride (II); followed by reduction and acidification to give hydrazine (III); b) *In situ* Reaction of the hydrazine hydrochloride (III) with ?-keto-?-valerolactone, to give the hydrazone (IV); c) Fischer indole synthesis of the hydrazone (IV), to give the pyranoindolone of formula (V); d) Transesterification of the pyranoindolone (V) to provide the compound (VI), in which R means a straight or branched C1-C4 alkyl; e) Conversion of the hydroxyl group of the compound (VI) into dimethylamino to give the indolecarboxylate (VII), in which R means a straight or branched C1-C4 alkyl; f) Saponification of the 2-carboalkoxy group of the compound (VII), to provide indolecarboxylic acid (VIII); g) Decarboxylation of the indolecarboxylic acid (VIII), to provide zolmitriptan and, eventually, to provide a pharmaceutically acceptable salt thereof.

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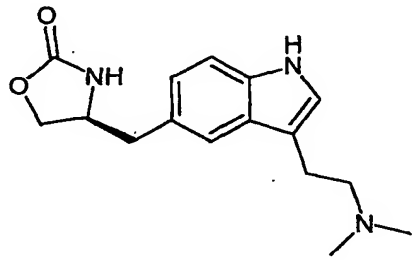
PROCESS FOR PREPARING ZOLMITRIPTAN COMPOUNDS

Field of the invention

This invention relates to a new process for preparing a pharmaceutically active compound. In particular, it relates to a process for preparing zolmitriptan.

Background of the invention

Patent ES 2104708 discloses a class of compounds with special agonism through the 5-HT_1-like receptors and excellent absorption following oral administration. These properties make the compounds particularly useful in the treatment of migraine, cluster headache and headache associated with vascular disorders. One of the preferred compounds of that patent is (S)-4-[3-(2-dimethylaminoethyl)-1H-indol-5-ylmethyl]-1,3-oxazolidin-2-one, known under the INN zolmitriptan, of formula (I):



(I)

The aforesaid patent describes the preparation of zolmitriptan by Fischer indole synthesis, using the corresponding phenyl hydrazine with an aldehyde. Said process nevertheless requires a stage of column

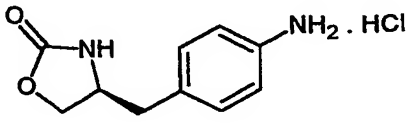
purification of the end product, as well as the use of toxic reagents such as tin chloride for preparing the hydrazine, while it has an overall yield of only 18%.

Later, European patent EP 843672 describes optimised preparation of the intermediate (S)-4-(4-aminobenzyl)-1,3-oxazolidin-2-one in a one pot process (that is, without isolating the intermediates) and preparation of the zolmitriptan on the basis of this intermediate in a second one pot process which includes the formation of the diazonium salt of the intermediate, followed by the Fischer reaction (by addition of 4,4-diethoxy-N,N-dimethylbutilamine). However, this patent does not quote the yield of zolmitriptan obtained. As a result, this applicant has carried out that procedure in order to reproduce and quantify it. The end product was obtained with yields of the order of 30% and with high impurity content due to the one pot reaction. It is therefore a process not applicable at industrial scale, either in terms of yield or of impurities.

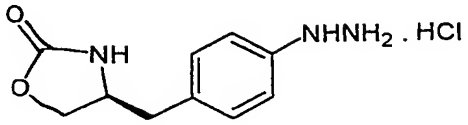
Description of the invention

A first aspect of the present invention is to provide a new process for preparing zolmitriptan or a pharmaceutically acceptable salt thereof, which comprises the following stages:

a) Preparation of the diazonium salt of the aniline hydrochloride of formula (II)

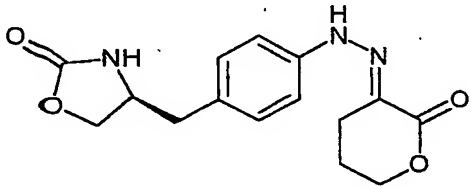


followed by reduction and acidification to give the hydrazine of formula (III):



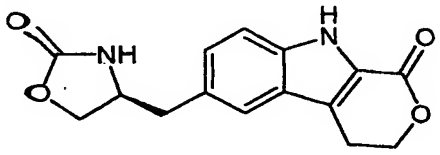
(III)

b) *In situ* reaction of the hydrazine hydrochloride of formula (III) with α-keto-δ-valerolactone to give the hydrazone of formula (IV):



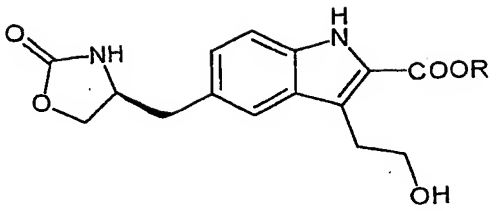
(IV)

c) Fischer indole synthesis of the hydrazone of formula (IV) to give the pyranoindolone of formula (V):



(V)

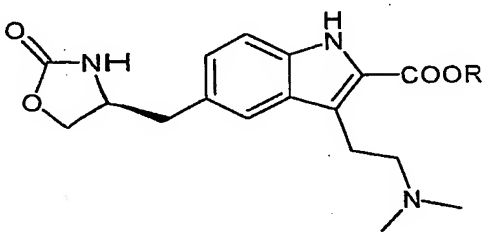
d) Transesterification of the pyranoindolone of formula (V), to provide the compound of formula (VI):



(VI)

in which R represents a straight or branched C1-C4 alkyl chain;

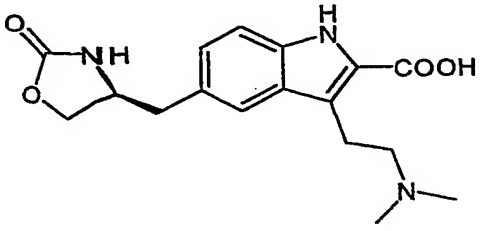
e) Conversion of the hydroxyl group of the compound of formula (VI) into dimethylamino, to give the indolecarboxylate of formula (VII):



(VII)

in which R represents a straight or branched C1-C4 alkyl chain;

f) Saponification of the 2-carboalkoxy group of the compound of formula (VII), to provide the indolecarboxylic acid of formula (VIII):



(VIII)

g) Decarboxylation of the indolecarboxylic acid of formula (VIII), to provide zolmitriptan and,

eventually, to prepare a pharmaceutically acceptable salt thereof.

Following, each of the steps of the general process for preparing zolmitriptan will be described in more detail.

Preparation of the diazonium salt of the aniline hydrochloride of formula (II), in stage a), is carried out by treating this compound with sodium nitrite and hydrochloric acid at low temperature. Subsequent reduction thereof is effected with an alkaline metal sulphite followed by acidification to give the hydrazine of formula (III).

Reaction of the hydrazine hydrochloride of formula (III) with α-keto-δ-valerolactone, in stage b), is carried out in aqueous medium at a temperature between 10°C and 80°C, preferably at room temperature, and at a pH between 0.1 and 4, preferably at pH 1. The product is isolated by conventional methods.

Stage c), to prepare the compound of formula (V), can be carried out at room temperature in a solution of dry hydrogen in acetic acid, and then the compound isolated by conventional methods.

The transesterification reaction of stage d) can then be carried out in an alcoholic solution, preferably methanol, and in the presence of an acid, preferably methanesulphonic acid. The product is isolated by conventional methods.

Alternatively, stage c) and stage d) can be carried out as a one pot reaction (that is, without isolating intermediates). In this case the Fischer indole synthesis of the hydrazone of formula (IV) followed by transesterification is carried out under conditions similar to those described in patent GB 1189064 for preparing carboalkoxy-indoles. It is thus preferably carried out in a solution of dry hydrogen chloride in a straight or branched C1-C4 alcohol chain (such as methanol, ethanol, etc.). The reaction can be carried out at a temperature between 0°C and 80°C, preferably between 60°C and 80°C, to prepare the compound of formula (VI), which is isolated by conventional methods.

Conversion of the hydroxyl group of the compound of formula (VI) into a dimethylamino group, in stage e), is carried out preferably by substituting the hydroxyl group by a leaving group X and subsequent substitution reaction of the leaving group X with dimethylamine. Preferably, X is a halogen atom, a mesylate group (OMs) or a tosylate group, a tosylate group being most preferable.

The replacement of the hydroxyl group of the compound of formula (VI) by a leaving group X can be carried out by reacting it with mesyl chloride or tosyl chloride or by replacing said hydroxyl by a halogen, using conventional halogenating reagents. It is carried out preferably by reaction with tosyl chloride. Thus, when X= OTs, the reaction is carried out in a suitable solvent, such as dichloromethane or toluene, in the presence of pyridine and of 4-(dimethylamino)pyridine as catalyst, and when X= OMs, the reaction is carried out in a suitable solvent, such as tetrahydrofuran, in the presence of triethylamine as catalyst. The reaction can be carried out at a temperature between 0°C and 50°C, preferably at room temperature. The product is isolated by conventional

methods.

In the case of the tosylates, the substitution reaction of the leaving group X with dimethylamine takes place under particularly gentle conditions. This reaction is carried out in an alcoholic solution or in an aqueous solution, at a temperature between 0°C and 100°C, preferably at 50°C. The product is isolated by conventional methods.

The saponification of the 2-carboalkoxy group of the compound of formula (VII), of stage f), is carried out in alkaline medium, preferably in an alcoholic solution of potassium hydroxide, and at a temperature between 20°C and 100°C, preferably at reflux temperature. The product is isolated by conventional methods.

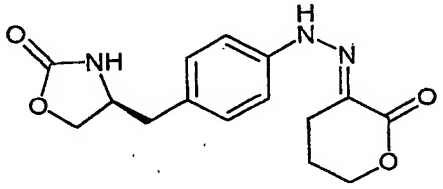
The decarboxylation of the indolecarboxylic acid of formula (VIII), of stage g), is carried out in the presence of an inert solvent of high boiling point and a suitable catalyst, in an inert atmosphere and at a temperature between 180°C and 250°C. Preferably, the solvent is quinoline or a mixture of quinoline and an organic solvent such as triethylene glycol dimethyl ether, diphenyl ether, etc. Catalysts can be chosen from powdered copper, cuprous oxide, cuprous chloride, cupric chromite, copper pentafluorophenyl or the cupric salt of the compound of formula (VIII) used in a molar proportion between 5% and 10% in relation to the compound of formula (VIII). The inert atmosphere can be created by stream of dry nitrogen. The reaction is preferably carried out at 200°C. The product is isolated by conventional methods.

The initial products for carrying out the process described above can be obtained as indicated below.

The aniline hydrochloride of formula (II) can be obtained by reduction of the corresponding nitro derivative, as described in patent ES 2104708, and the α-keto-δ-valerolactone can be obtained by decarboxylation of α-ethoxyalyl-γ-butyrolactone in 2N H_2SO_4 at reflux.

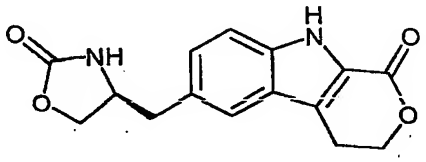
The present invention also relates to the synthesis intermediates useful for preparing zolmitriptan.

A second aspect of the present invention is the synthesis intermediate of formula (IV):



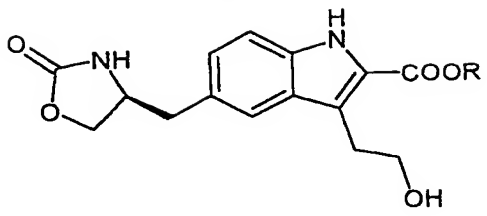
(IV)

A third aspect of the present invention is the synthesis intermediate of formula (V):



(V)

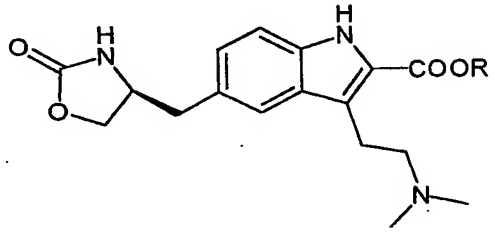
A fourth aspect of the present invention is a synthesis intermediate of formula (VI):



(VI)

in which R represents a straight or branched C1-C4 alkyl chain.

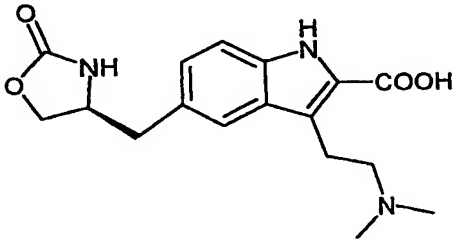
A fifth aspect of the present invention is a synthesis intermediate of formula (VII):



(VII)

in which R has the meaning defined above.

A sixth aspect of the present invention is the intermediate synthesis intermediate of formula (VIII):



(VIII)

The aforesaid synthesis intermediates of formula (IV), (V), (VI), (VII) and (VIII) are useful for the synthesis of zolmitriptan, although their use for synthesis of other products likewise forms part of the scope of protection of the present invention.

The stages described above in the general process for providing zolmitriptan can therefore be considered independent processes for preparing the intermediate synthesis products, isolating the intermediate product where necessary.

There follows a description of these stages as independent procedures for preparing each one of the synthesis intermediates.

- A first process relates to preparation of the intermediate of formula (IV) by reaction of the hydrazine hydrochloride of formula (III) with α-keto-δ-valerolactone, in accordance with stage b) of the first aspect of the invention.

- A second process relates to preparation of the intermediate of formula (V) by Fischer indole synthesis of the hydrazone of formula (IV), in accordance with stage c) of the first aspect of the invention.

- A third process relates to preparation of the intermediate of formula (VI), by transesterification of the pyranoindolone of formula (V), in accordance with stage d) of the first aspect of the invention.

- A fourth process relates to preparation of the intermediate of formula (VII), by conversion of the hydroxyl group of the compound of formula (VI) into

dimethylamino, in accordance with stage e) of the first aspect of the invention.

- A fifth process relates to preparation of the intermediate of formula (VIII), by saponification of the 2-carboalkoxy group of the intermediate of formula (VII), in accordance with stage f) of the first aspect of the invention.

For a better understanding of what is outlined some examples are included which, in a non-restrictive manner, show practical cases of embodiment of the invention.

EXAMPLES OF SYNTHESIS

Example 1: (S)-4-{4-[*N'*-(2-Oxotetrahydropyran-3-iliden)hidrazino]benzyl}-1,3-oxazolidin-2-one

A solution of 2.8 g (40.6 nmoles) of sodium nitrite in 12 ml of water was added slowly to a solution of 9.1 g (39.8 mmoles) of (S)-4-(4-aminobenzyl)-1,3-oxazolidyne-2-one hydrochloride in 17 ml of water and 29 ml of concentrated HCl, keeping the reaction temperature below 0°C. The mixture was stirred at this temperature for 15 minutes. Once that time had elapsed the diazonium salt solution was added rapidly to a suspension of 30 g (239 mmoles) of sodium sulphite in 106 ml of water precooled to 0°C under nitrogen atmosphere. The red solution was stirred at 0 °C for 10 minutes and then left to reach 65 °C in 1 hour. It was stirred at 65 °C for 30 minutes, and 18.2 ml of concentrated HCl then added. The mixture was stirred at the same temperature under nitrogen atmosphere for 3 hours and then left to cool to room temperature. To this solution was added a solution of 63.7 mmoles of α-keto-δ-valerolactone (prepared by

decarboxylation of 11.8 g (63,7 mmoles) of α-ethoxyalyl-γ-butyrolactone in 15.2 ml of 2N H_2SO_4 at reflux) and left under stirring at room temperature for 12 hours. When that time had elapsed the mixture was cooled to 0°C and stirred for one hour. The precipitate formed was filtered, washed with cold water and dried in an hot-air oven at 40°C, giving a white solid which was crystallised from ethanol/water to give 10.5 g (87%) of the title hydrazone as a white solid.

M.p. 223.3-224.7 °C.

IR (KBr): 1127 cm^{-1}, 1250 cm^{-1}, 1400 cm^{-1}, 1422 cm^{-1}, 1544 cm^{-1}, 1694 cm^{-1}, 1755 cm^{-1}.

^{1}H-NMR(200 MHz, DMSO-d_6): 1.99 (m, 2H, γ-lactone); 2.59 (m, 4H, β-lactone and CH_2-benz.); 3.98 (m, 2H, OCH_2); 4.27 (m, 3H, δ-lactone and NHCH); 7.14 (d, 2H, *J*=8.4 Hz, ar); 7.24 (d, 2H, *J*=8.4 Hz, ar); 7.77 (s, 1H, CONH); 10.03 (s, 1H, NH-hydrazone).

^{13}C-NMR(200 MHz, DMSO-d_6): 21.3; 24.5; 52.8; 67.5; 68.2; 114.3; 129.5; 130.2; 130.4; 143.0; 158.8; 162.3.

Example 2: (S)-6-(2-Oxo-1,3-oxazolidin-4-ylmethyl)-4,9-dihydro-3*H*-pyrano-[3,4-b]indol-1-one

3.8 g (12.5 mmoles) of (S)-4-{4-[*N'*-(2-oxotetrahydropyran-3-iliden)hydrazine]benzyl}-1,3-oxazolidin-2-one were suspended in 32 ml of a saturated solution of hydrogen chloride in acetic acid. The mixture was stirred at room temperature for 16 h, 10 ml of water/ice was added to the reaction mixture and stirred at 0°C for 20 min. The precipitate was filtered, washed with cold water and dried in hot-air oven at 40°C. The residue

was crystallised with methanol to yield 3.3 g (92%) of the title indole as a yellow crystalline solid.

M.p. 215-217 °C.

IR (KBr): 1400, 1705, 1733, 3355 cm^{-1}.

^{1}H-NMR (200 MHz, DMSO-d_6): 2.85 (t, *J*=4,8 Hz, 2H, CH_2-benz.); 3.09 (t, *J*=6.4 Hz, 2H, δ-lactone); 4.04 (m, 2H, OCH_2); 4.26 (m, 1H, NHCH); 4.62 (t, *J*=6.4 Hz, 2H, γ-lactone); 7.21 (d, *J*=8,6 Hz, 1H, ar); 7.36 (d, *J*=8.6 Hz, 1H, ar); 7.55 (s, ar), 7.81 (s, 1H, CONH); 11.88 (s, 1H, NH-indole).

^{13}C-NMR (200 MHz, DMSO): 21.0; 53.0; 68.2; 69.2; 112.9; 121.3; 122.2; 122.6; 124.4; 127.9; 128.3; 137.3; 158.8; 160.5.

Example 3: (S)-3-(2-Hydroxyethyl)-5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1*H*-indol-2-carboxylic acid methyl ester

To a suspension of 500 mg (1.74 mmoles) of the (S)-6-(2-oxo-1,3-oxazolidin-4-ylmethyl)-4,9-dihydro-3*H*-pyrano-[3,4-b]indol-1-one in 10 ml of methanol were added 0.12 ml (1.9 mmoles) of methanesulphonic acid. The mixture was left under stirring at the reflux temperature for 3 hours. The solvent was evaporated to dryness under reduced pressure, the residue dissolved with 10 ml of a saturated bicarbonate solution and extracted three times with dichloromethane. The combined organic phases were dried and evaporated to dryness and the evaporated solid recrystallised from ethanol to give 517 mg (93%) of the title ester as a yellow crystalline solid.

M.p. 178-180 °C.

IR (KBr): 1427, 1555, 1695, 1738, 3354 cm^{-1}.

^{1}H-NMR (200 MHz, DMSO-d_6): 2,85 (m, 2H, CH_2-benz.); 3.21 (m, 2H, CH_2CH_2OH); 3.60 (m, 2H, CH_2CH_2OH); 3.87 (s, 3H, CH_3); 4.03 (m, 2H, OCH_2); 4.26 (m, 1H, NHCH); 4.67 (t, *J*=5.2 Hz, 1H, OH); 7.13 (d, *J*= 8,4 Hz, 1H, ar); 7.33 (d, *J*=8.4 Hz, 1H, ar); 7.54 (s, 1H, ar); 7.82 (s, 1H, CONH); 11.47 (s, 1H, NH-indole).

Example 4: (S)-3-(2-Hydroxyethyl)-5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1*H*-indol-2- carboxylic acid ethyl ester

9.5 g (31.3 mmoles) of S)-4-{4-[*N'*-(2-oxotetrahydropyran-3-ilyden)hydrazine]benzyl}-1,3-oxazolidin-2-one were suspended in 76 ml of a 2N solution of hydrogen chloride in absolute ethanol. The mixture was left under stirring at 75 °C for 30 min. The solvent was evaporated to dryness under reduced pressure, 50 ml of a saturated solution of potassium carbonate added, and then extracted three times with 50 ml of dichloromethane. The combined organic phases were dried on anhydrous sodium sulphate and evaporated to dryness. The residue was recrystallised from isopropyl alcohol/heptane to give 9.25 g (89%) of the title indole. The product was recrystallised from methanol to give a yellow crystalline solid.

M.p. 154-156 °C.

IR (KBr): 1244 cm^{-1}, 1688 cm^{-1}, 1744 cm^{-1}, 3300 cm^{-1}.

^{1}H-NMR (200 MHz, DMSO-d_6): 1.34 (t, *J*=7.0 Hz, 3H, OCH_2CH_3); 2.84 (m, 2H, CH_2-benz.); 3.20 (m, 2H, CH_2CH_2OH); 3.58 (m, 2H, CH_2CH_2OH); 4,02 (m, 2H, OCH_2); 4.31 (m, 3H, OCH_2CH_3 and NHCH); 4,65 (t, *J*=5.4 Hz, 1H, OH); 7.12 (dd, *J*=0.8 and 8.4 Hz. 1H, ar); 7.33 (d, *J*=8.4 Hz, 1H, ar); 7.52 (s, 1H, ar); 7.81 (s, 1H, CONH); 11.41 (s, 1H, NH-indole).

^{13}C-NMR (200 MHz, DMSO-d_6): 15.0; 29.2; 41.2; 53.7; 60.8; 62.4; 68.8; 113.1; 120.6; 121.5; 124.3; 127.4; 128.1; 128.5; 136.0; 159.4; 162.4.

Example 5: (S)-5-(2-Oxo-1,3-oxazolidin-4-ylmethyl)-3-[(2-toluen-4-sulphonyloxy)ethyl]-1*H*-indol-2-carboxylic acid ethyl ester

To a stirred suspension of 4.6 g (13.8 mmoles) of the (S)-3-(2-hydroxyethyl)-5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1*H*-indol-2- carboxylic acid ethyl ester in 42 ml of dichloromethane were added 4.2 ml of pyridine, 3.9 g (20.7 mmoles) of tosyl chloride and 170 mg (1.38 mmoles) of dimethylaminopyridine and the stirring continued at room temperature for 20 hours. The reaction mixture was poured over 20 ml of 3N HCl precooled to 0°C and extracted twice with 40 ml of dichloromethane. The combined organic phases were washed with brine, dried on anhydrous sodium sulphate and the solvent evaporated to dryness. The evaporated solid was crystallised with isopropyl alcohol to give 6.4 g (95%) of the title compound as a white crystalline solid.

M.p. 166.4-168.2 °C.

IR(KBr):1154 cm^{-1}, 1238 cm^{-1}, 1312 cm^{-1}, 1705 cm^{-1}, 1722 cm^{-1}, 1766 cm^{-1}.

^{1}H-NMR(200 MHz, DMSO-d_6): 1.28 (t, *J*=72 Hz, 3H, $OCH_2\underline{CH_3}$); 2.37 (s, 3H, CH_3); 2.82 (m, 2H, $\underline{CH_2}CH_2OTs$); 332 (t, *J*=6,4 Hz, 2H, CH_2-benz.); 400 (m, 3H, $CH_2\underline{CH_2}OTs$ and NH$\underline{CH}$); 4.25 (4H, m, $O\underline{CH_2}CH_3$ and OCH_2); 7.13 (d, *J*=8,4 Hz, 1H, ar); 7.38 (m, 6H, ar); 7.82 (s, 1H, CONH); 11.56 (s, 1H, NH-indole).

^{13}C-NMR (200 MHz, DMSO-d_6): 14.3; 21.2; 24.3; 40.6; 53.11; 60.4; 68.2; 70.4; 112.6; 116.5; 120.4; 126.9; 127.3; 127.6; 127.8; 129.9; 132.2; 135.2; 144.7; 158.8; 161.4.

Example 6: (S)-3-(2-Dimethylaminoethyl)-5-[2-oxo-1,3-oxazolidin-4-ylmethyl]-1*H*-indol-2-carboxylic acid ethyl ester

A stirred suspension of 5 g (10,3 mmoles) of (S)-5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-3-[(2-toluen-4-sulphoniloxy)ethyl]-1*H*-indol-2-carboxylic acid ethyl ester in 30 ml of a 2N solution of dimethylamine in ethanol was stirred at 50°C for 20 hours in a closed reactor. The solvent was evaporated to dryness, the residue dissolved in 20 ml of 2N HCl and washed three times with 15 ml of dichloromethane. The washed aqueous phase was cooled and adjusted to pH 12 with a 40% sodium hydroxide solution and extracted three times with 20 ml of dichloromethane. The combined organic phases were washed with brine and dried on anhydrous sodium sulphate. The solvent was evaporated to dryness and the residue recrystallised from ethyl acetate to give 3.4 g (91%) of the title dimethylamine as a yellow solid.

M.p. 67-70 °C.

IR (KBr): 1333 cm^{-1}, 1711 cm^{-1}, 1745 cm^{-1}.

^{1}H-NMR(200 MHz, DMSO-d_6): 1.35 (t, J=7,0 Hz, 3H, $OCH_2\underline{CH_3}$); 2.23 (S, 6H, $N(CH_3)_2$); 2.45 (m, 2H, $\underline{CH_2}CH_2N$); 2.86 (m, 2H, $CH_2\underline{CH_2}N$); 3.18 (m, 2H, CH_2-benz.); 4.05 (m, 2H, OCH_2); 4.34 (m, 3H, OCH_2CH_3 and NHCH); 7.14 (dd, J=1,2 and 8.4 Hz, 1H, ar); 7.35 (d, J=8,4 Hz, 1H, ar); 7.52 (s, 1H, ar); 7.82 (s, 1H, CONH); 11.47 (s, 1H, NH-indole).

^{13}C-NMR (200 MHz, DMSO-d_6): 14.5; 22.5; 40.9; 45.2; 53.1; 60.2; 60.3; 68.1; 112.5; 120.7; 121.1; 123.5; 126.9; 127.5; 127.6; 135.5; 158.8; 161.9.

Example 7: (S)-3-(2-Dimethylaminoethyl)-5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1*H*-indol-2-carboxylic acid

To a solution of 1.4 g (24.9 mmoles) of KOH in 30 ml of ethanol was added 2.8 g (7.8 mmoles) of (S)-3-(2-dimethylaminoethyl)-5-[2-oxo-1,3-oxazolidin-4-ylmethyl]-1*H*-indol-2-carboxylic acid ethyl ester. The resulting solution was heated at reflux temperature for one hour. It was cooled and the solvent evaporated to dryness. The residue was dissolved in 6 ml of water and washed three times with 10 ml of dichloromethane. The aqueous solution was cooled to 5°C, adjusted to pH 6 with glacial acetic acid, stirred for 30 minutes at that temperature and the water evaporated to dryness. The residue was redissolved in 30 ml of water and 5 g of ionic exchange resin (Dowex 50WX8-400) added. The mixture was left under stirring at room temperature for 24 hours. The resin was filtered and it was washed with water. For desorption the resin was suspended with 20 ml of a 10% aqueous solution of ammonia and stirred at room temperature for 5 hours. Once that time had elapsed it was filtered and washed with water. The water was evaporated to dryness under reduced pressure to give 7.75 g (94%) of the title acid as a yellow crystalline solid.

M.p. 230 °C.

IR (KBr): 1342 cm^{-1}, 1403 cm^{-1}, 1587 cm^{-1}, 1739 cm^{-1}, 3430 cm^{-1}.

^{1}H-NMR(200 MHz, DMSO-d_6): 2.47 (s, 6H. $N(CH_3)_2$), 2.87 (m, 4H, CH_2CH_2N), 3.27 (m, 2H, CH_2-benz.); 4.03 (m, 2H, OCH_2); 4.27 (m, 1H, NHCH), 6.98 (d, *J*=8,0 Hz, 1H, ar), 7.27 (d, *J*=8,0 Hz, 1H, ar), 7.41 (s, 1H, ar); 7.83 (s, 1H, CONH), 10.95 (s, 1H, NH-indole).

^{13}C-NMR (200 MHz, DMSO-d_6): 21.15; 43.7; 53.3; 59.7; 68.2; 112.1; 113.2; 119.7; 124.4; 126.4; 128.1; 132.2; 134.0; 158.9; 166.2.

Example 8: (S)-4-[3-(2-Dimethylaminoethyl)-1*H*-indol-5-ylmethyl]-1,3-oxazolidin-2-one

1 g (3.02 mmoles) of the (S)-3-(2-dimethylaminoethyl)-5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1*H*-indol-2-carboxylic acid was suspended in 10 ml of dry quinoline. 20 mg of cuprous oxide was added and the stirred suspension heated to 200 °C under dry nitrogen stream. The reaction mixture was kept at this temperature until no more CO_2 was released (15-20 min.). It was left to cool to room temperature and the reaction mixture filtered through decalite. The filtrate was concentrated by vacuum distillation of the solvent, providing a residue which was dissolved with a succinic acid solution and washed three times with 15 ml of dichloromethane. The washed aqueous phase was cooled, the pH adjusted to 12 with a 40% sodium hydroxide solution and extracted three times with 20 ml of dichloromethane. The combined organic phases were dried on anhydrous sodium sulphate and evaporated to dryness. The residue was recrystallised with isopropyl alcohol to give 780 mg (90%) of zolmitriptan as a white solid.

M.p. 138-140 °C.

IR (KBr): 1237 cm^{-1}, 1443 cm^{-1}, 1743 cm^{-1}.

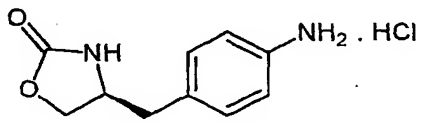
^{1}H-NMR(200 MHz, $CDCl_3$): 2.34 (s, 6H, $N(CH_3)_2$), 2.67 (m, 2H, $C\underline{H}_2CH_2N$), 2.93 (t, 4H, $CH_2C\underline{H}_2N$ and CH_2-benz.), 4.14 (m, 2H, OCH_2), 4.43 (m, 1H, $NHC\underline{H}$); 5.60 (ba, 1H, NH-indole); 6.94 (dd, J=1,2 and 8.6 Hz, 1H, ar); 7.01 (d, J=1,2 Hz, 1H, ar); 7.28 (d, J=8.6 Hz, 1H, ar), 7.37 (s, 1H, ar), 8.49 (s, 1H, CONH).

^{13}C-NMR (200 MHz, $CDCl_3$): 23,5; 41,6; 45,3; 54,3; 60,1; 67,7; 111,6; 113,8; 118,8; 122,4; 122,7; 126,4; 127,8; 135,4; 159,3.

C L A I M S

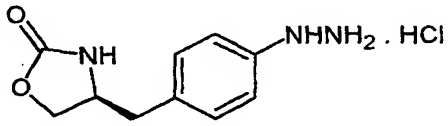
1. Process for preparing a pharmaceutically active compound, zolmitriptan, or a pharmaceutically acceptable salt thereof, **characterised** in that it comprises the following stages:

a) Preparation of the diazononium salt from the aniline hydrochloride of formula (II)



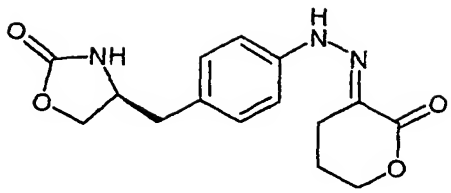
(II)

followed by reduction and acidification to give the hydrazine of formula (III):



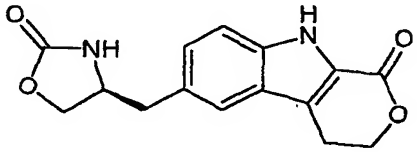
(III)

b) *In situ* reaction of the hydrazine hydrochloride of formula (III) with α-keto-δ-valerolactone, to give the hydrazone of formula (IV):



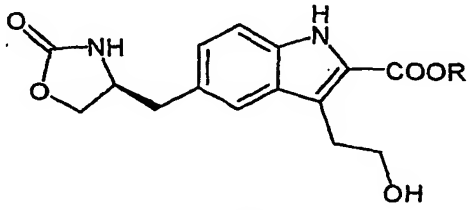
(IV)

c) Fischer indole synthesis of the hydrazone of formula (IV), to give the pyranoindolone of formula (V):



(V)

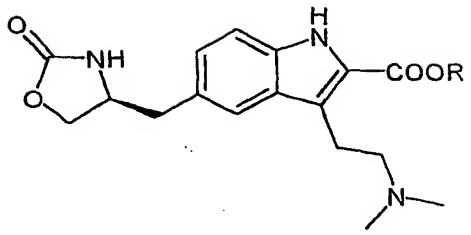
d) Transesterification of the pyranoindolone of formula (V), to provide the compound of formula (VI):



(VI)

in which R represents a straight or branched C1-C4 alkyl chain;

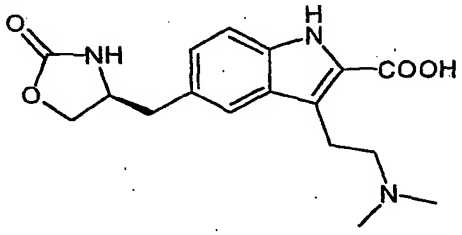
e) Conversion of the hydroxyl group of the compound of formula (VI) into dimethylamino, to give the indolecarboxylate of formula (VII):



(VII)

in which R represents a straight or branched C1-C4 alkyl chain;

f) Saponification of the 2-carboalkoxy group of the compound of formula (VII), to give the indolecarboxylic acid of formula (VIII):



(VIII)

g) Decarboxylation of the indolecarboxylic acid of formula (VIII), to give zolmitriptan and,

eventually, the preparation of a pharmaceutically acceptable salt thereof.

2. Process as claimed in Claim 1, characterised in that said stage c) is carried out in a solution of dry hydrogen chloride in acetic acid.

3. Process as claimed in Claim 1, characterised in that said stages c) and d) are carried out in a one pot reaction.

4. Process as claimed in Claim 1 and Claim 3, characterised in that said stages c) and d) are carried out in a solution of dry hydrogen chloride in a straight or branched C1-C4 alcohol chain.

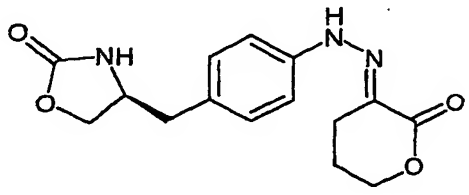
5. Process as claimed in Claim 1, characterised in that said stage e) is carried out in two steps:

e-i) replacement of the hydroxyl group of the compound of formula (VI) by a leaving group X; and

e-ii) subsequent substitution reaction of the leaving group X with dimethylamine to provide the compound of formula (VII).

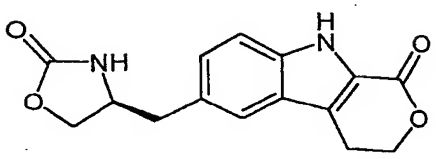
6. Process as claimed in Claim 5, characterised in that said leaving group X is chosen between an atom of halogen, a mesylate group or a tosylate group.

7. Synthesis intermediate of formula (IV):



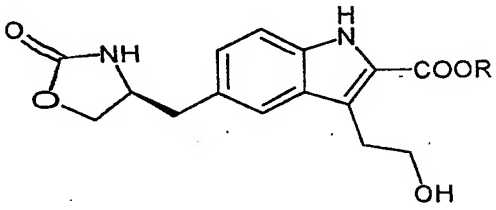
(IV)

8. Synthesis intermediate of formula (V):



(V)

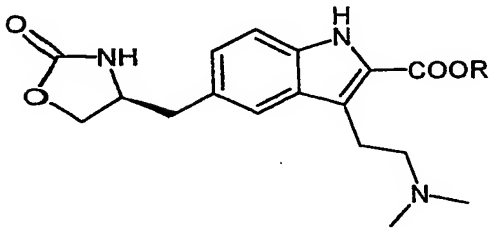
9. Synthesis intermediate of formula (VI):



(VI)

where R represents a straight or branched C1-C4 alkyl chain.

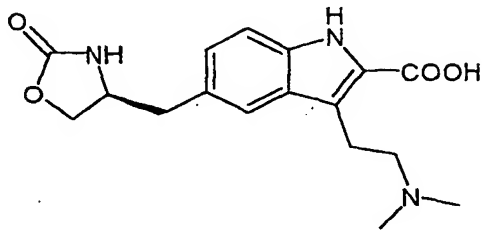
10. Synthesis intermediate of formula (VII):



(VII)

where R represents a straight or branched C1-C4 alkyl chain.

11. Synthesis intermediate of formula (VIII):



(VIII)

INTERNATIONAL SEARCH REPORT

PCT/IB 03/03536

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D413/12 C07D413/06 C07D491/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal, WPI Data, BEILSTEIN Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MOLONEY, GERARD P. ET AL: "A Novel Series of 2,5-Substituted Tryptamine Derivatives as Vascular 5HT1B/1D Receptor Antagonists" JOURNAL OF MEDICINAL CHEMISTRY (1997), 40(15), 2347-2362 , XP002260072 compound 3	10
A	Scheme 2	1-9,11
A	WO 91 18897 A (WELLCOME FOUND) 12 December 1991 (1991-12-12) page 7 -page 25; claim 17	1-11
A	WO 97 06162 A (WELLCOME FOUND ;PATEL RAJNIKANT (GB)) 20 February 1997 (1997-02-20) claim 1	1-11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 November 2003	20/11/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seelmann, I

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9118897 A	12-12-1991	AT 156823 T	15-08-1997
		AT 204275 T	15-09-2001
		AU 646871 B2	10-03-1994
		AU 7957091 A	31-12-1991
		CA 2064815 A1	08-12-1991
		CA 2282890 C	31-07-2001
		CS 9101727 A3	19-02-1992
		DE 69127260 D1	18-09-1997
		DE 69127260 T2	04-12-1997
		DE 69132691 D1	20-09-2001
		DE 69132691 T2	20-06-2002
		DK 486666 T3	30-03-1998
		EG 19650 A	30-09-1995
		EP 0486666 A1	27-05-1992
		EP 0636623 A1	01-02-1995
		ES 2104708 T3	16-10-1997
		FI 105686 B1	29-09-2000
		FI 960155 A	12-01-1996
		FI 20001406 A	13-06-2000
		WO 9118897 A1	12-12-1991
		GR 3024828 T3	30-01-1998
		HK 1000534 A1	03-04-1998
		HR 940524 A1	30-06-1996
		HU 62289 A2	28-04-1993
		HU 9500532 A3	30-10-1995
		IE 911931 A1	18-12-1991
		IE 20010862 A1	05-03-2003
		IL 98392 A	19-01-1996
		IL 114690 A	18-02-1997
		JP 2738461 B2	08-04-1998
		JP 5502679 T	13-05-1993
		KR 215627 B1	16-08-1999
		LT 419 A ,B	25-11-1994
		LU 90205 A9	06-04-1998
		LV 10274 A ,B	20-10-1994
		MC 2210 A	26-11-1992
		MX 9203421 A1	01-07-1992
		NO 920494 A	30-03-1992
		NZ 238424 A	23-12-1993
		PL 166214 B1	28-04-1995
		PT 97888 A ,B	29-05-1992
		RU 2160736 C2	20-12-2000
		SG 52664 A1	28-09-1998
		SI 9111010 A	31-12-1997
		SK 281621 B6	10-05-2001
		RU 2110517 C1	10-05-1998
		US 5466699 A	14-11-1995
		US 5863935 A	26-01-1999
		US 5399574 A	21-03-1995
		ZA 9104340 A	24-02-1993
WO 9706162 A	20-02-1997	AT 227723 T	15-11-2002
		AU 718413 B2	13-04-2000
		AU 6663496 A	05-03-1997
		BR 9609830 A	09-03-1999
		CA 2227039 A1	20-02-1997
		CN 1317480 A	17-10-2001
		CN 1403455 A	19-03-2003

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 03/03536

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9706162 A		CN 1201460 A ,B	09-12-1998
		CZ 9800352 A3	17-06-1998
		DE 69624825 D1	19-12-2002
		DE 69624825 T2	04-09-2003
		DK 843672 T3	17-02-2003
		EP 1227095 A2	31-07-2002
		EP 0843672 A1	27-05-1998
		ES 2185790 T3	01-05-2003
		WO 9706162 A1	20-02-1997
		HK 1009129 A1	02-05-2003
		HU 9900188 A2	28-05-1999
		IN 185148 A1	25-11-2000
		JP 11513023 T	09-11-1999
		JP 2002037786 A	06-02-2002
		JP 2002097178 A	02-04-2002
		JP 2002308858 A	23-10-2002
		NO 980522 A	06-02-1998
		NO 20005187 A	06-02-1998
		NZ 315040 A	28-01-2000
		PL 324881 A1	22-06-1998
		PT 843672 T	31-03-2003
		RU 2167875 C2	27-05-2001
		SI 843672 T1	30-04-2003
		SK 15498 A3	03-06-1998
		TR 9800182 T1	21-05-1998
		US 6084103 A	04-07-2000
		US 6160123 A	12-12-2000
		ZA 9606711 A	18-02-1997